

Folate Reductase Inhibitor

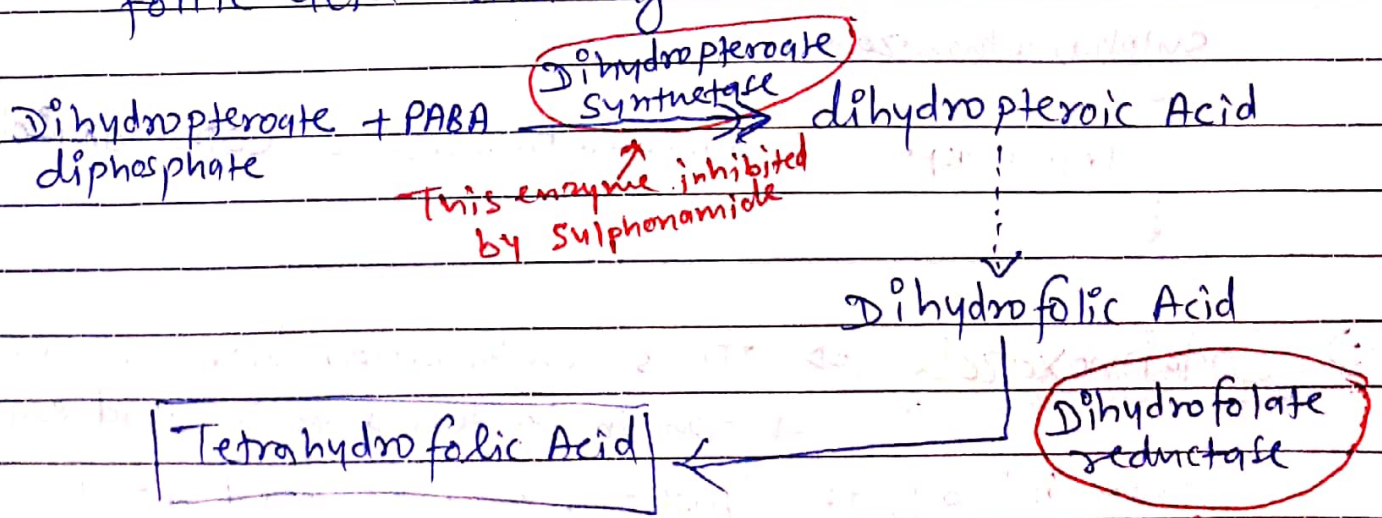
Compounds/molecule that inhibits the function of dihydrofolate reductase enzyme is called dihydrofolate reductase inhibitors (DHFR).

⇒ Because folic acid or folate is needed by rapidly dividing cell to make thymine (a nucleotide) in our body

⇒ Bacteria also need folic acid to make its nucleic acid.

⇒ Humans get their folic acid from the diet

⇒ But bacterial cell synthesize their own folic acid utilizing PABA



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This enzyme inhibited by DHFR inhibitors such as Trimethoprim

Examples Trimethoprim → Inhibitor of bacterial DHFR

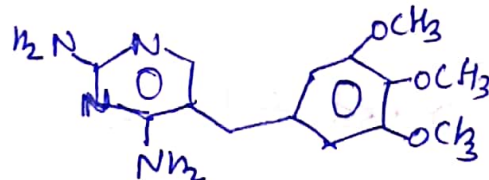
Pyrimethamine → Inhibitor of Plasmodium DHFR

Methotrexate → Inhibitor of human DHFR
(used in cancer treatment)

Proguanil → is a prodrug metabolised by enzyme to generate active drug Cycloguanil

it is inhibitor of malarial plasmodium DHFR

Trimethoprim :



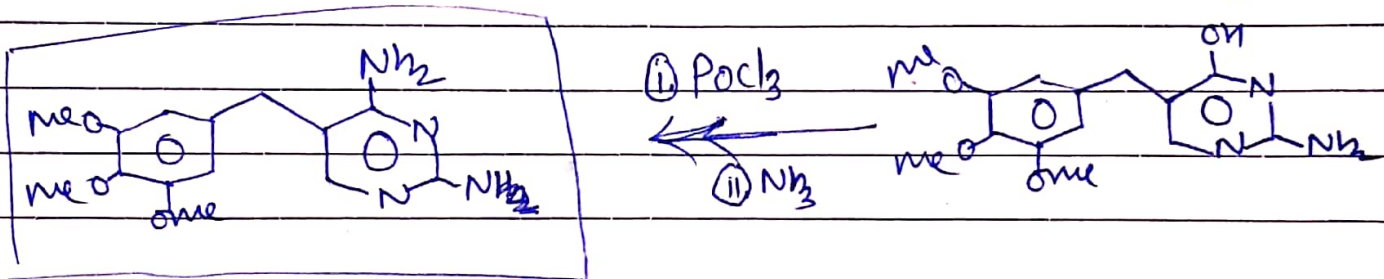
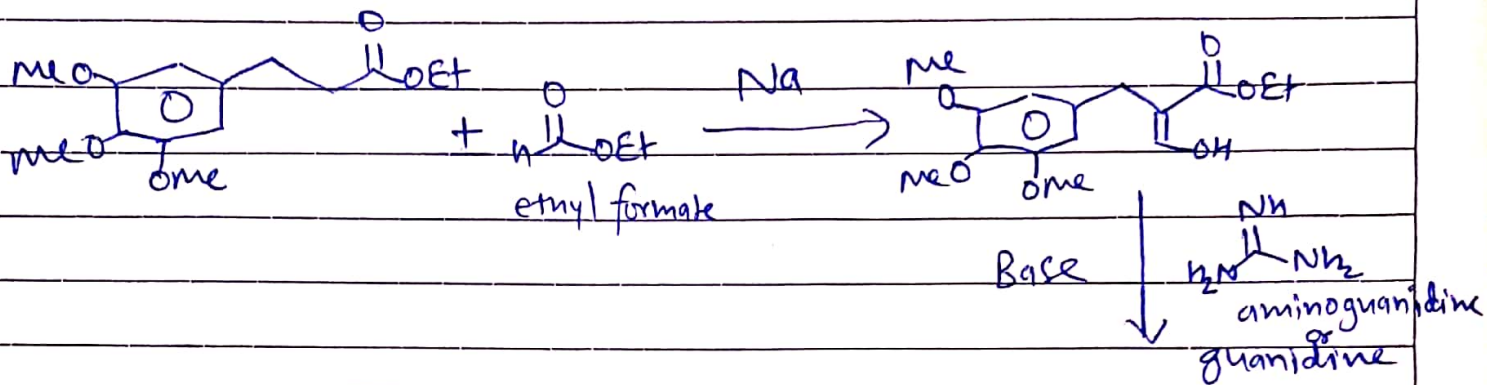
- ⇒ It inhibit bacterial DHFR enzyme.
- ⇒ If used alone, bacteria can get resistant to this drug.
- ⇒ So, trimethoprim used with sulfonamide drug sulphamethoxazole.

Trimethoprim + Sulphamethoxazole = Cotrimoxazole

⇒ Cotrimoxazole ⇒ This combination have dual action in bacterial folic acid synthesis

They inhibit, the synthesis of folic acid at two site —

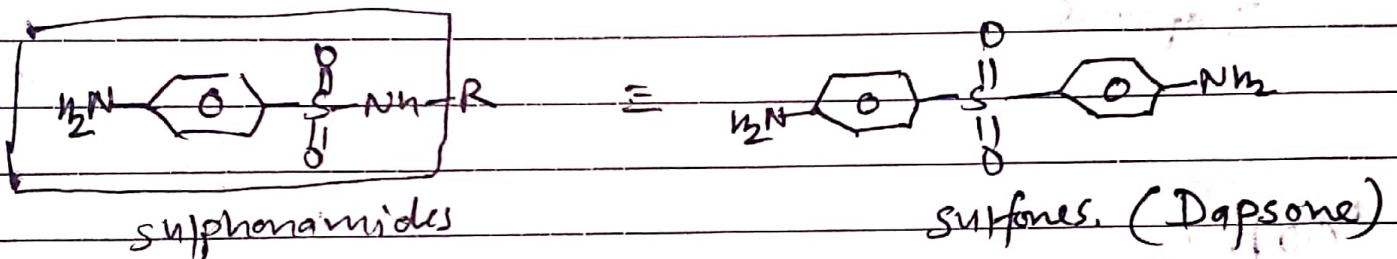
- (1) Dihydropteroate synthetase - by sulphamethoxazole
- (2) Dihydrofolate reductase - by trimethoprim

Synthesis of Trimethoprim

Trimethoprim

Sulfones

They are similar to sulphonamides but differ from the basic sulphonamide nucleus. They possess anti-bacterial properties.

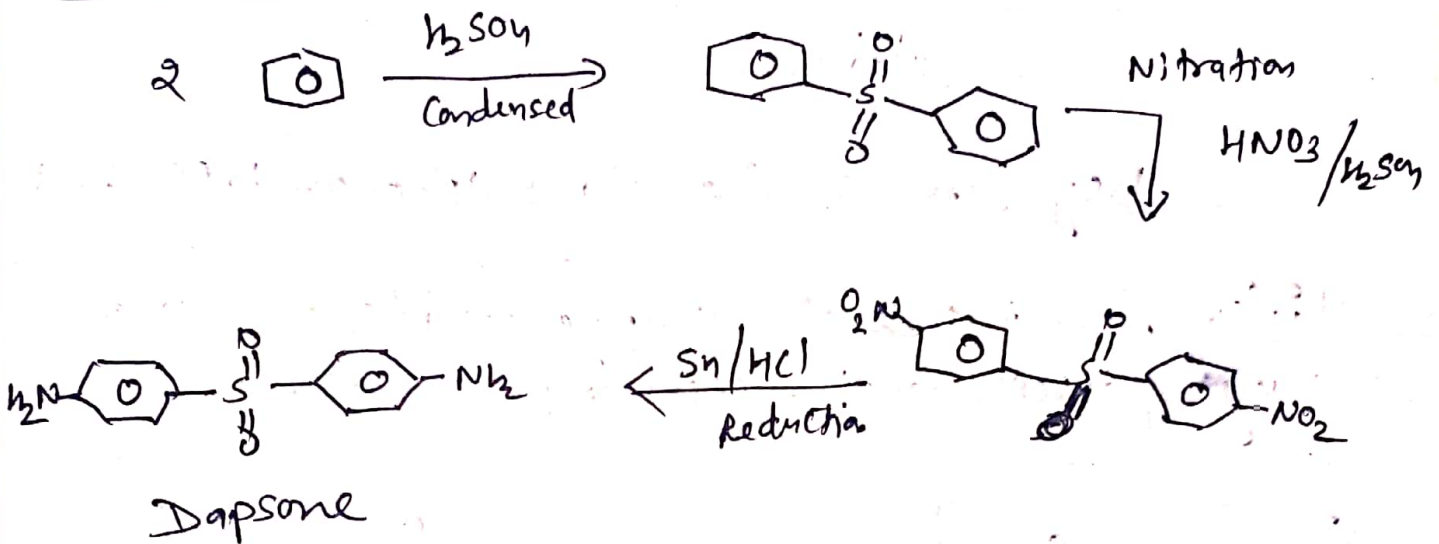


Dapsone: It shows an antibacterial spectrum and MOA similar to sulphanilamides.

- ⇒ It is the drug of choice in chemotherapy for leprosy.
- ⇒ It is also used for the treatment of nocardiosis.
- ⇒ Dose 25 mg twice a week initially for one month ~~for~~ as leprostatic action, followed by 25 mg/day for each month.

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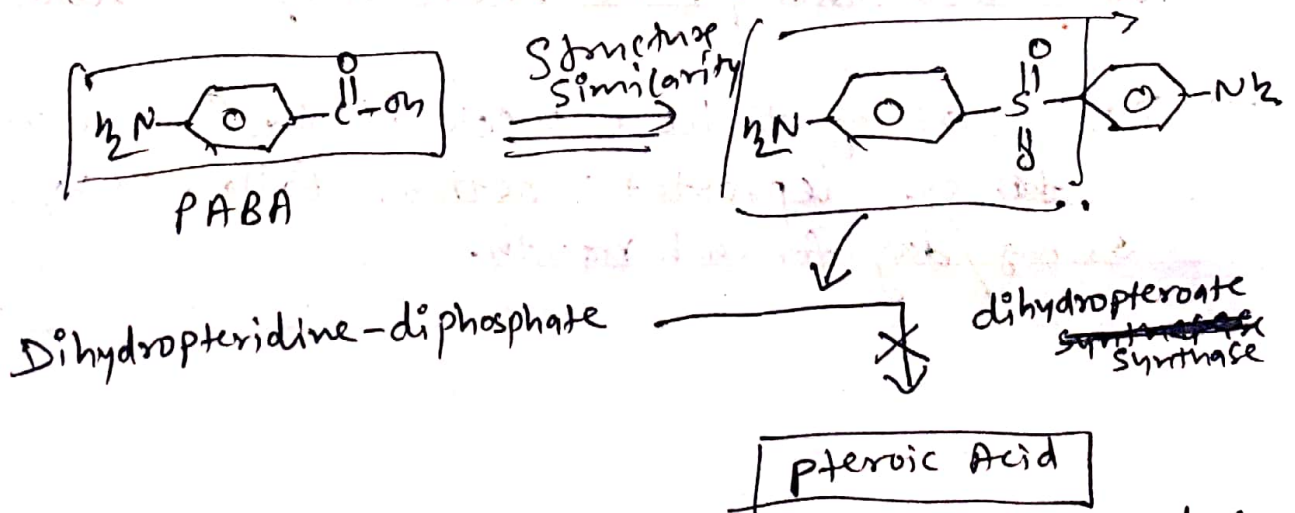
Synthesis !



MOA !

⇒ It inhibits synthesis of bacterial dihydrofolic acid through competition with PABA (para- amino benzoic acid).

⇒ It binds at the active site of ~~dihydrofolate~~ dihydropteroate synthase and inhibits bacterial nucleic acid synthesis.



No synthesis of pteronic acid which is required for folic acid synthesis.